? predict.

prevent.

Precocious puberty

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Head of Pediatric Endocrinology Unit

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Gonadotropic axis

Central Nervous System
Stimulatory and inhibitory
neurotransmitter/neurosteroids
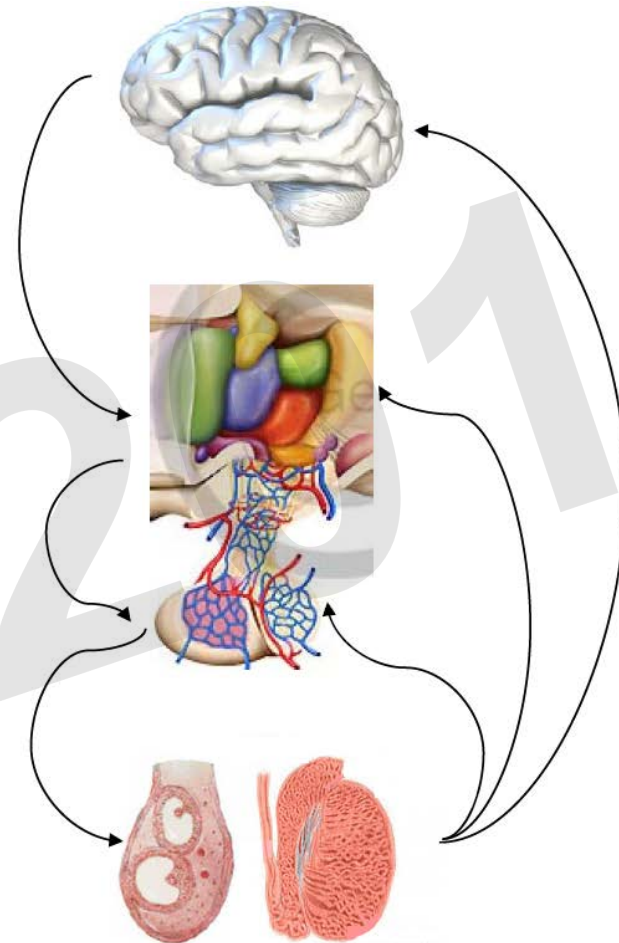Growth factors

Hypothalamus
Gonadotropin-Releasing Hormone
(GnRH=LHRH)

Pituitary
Follicle stimulating hormone (FSH)
Luteinising hormone (LH)

Gonads
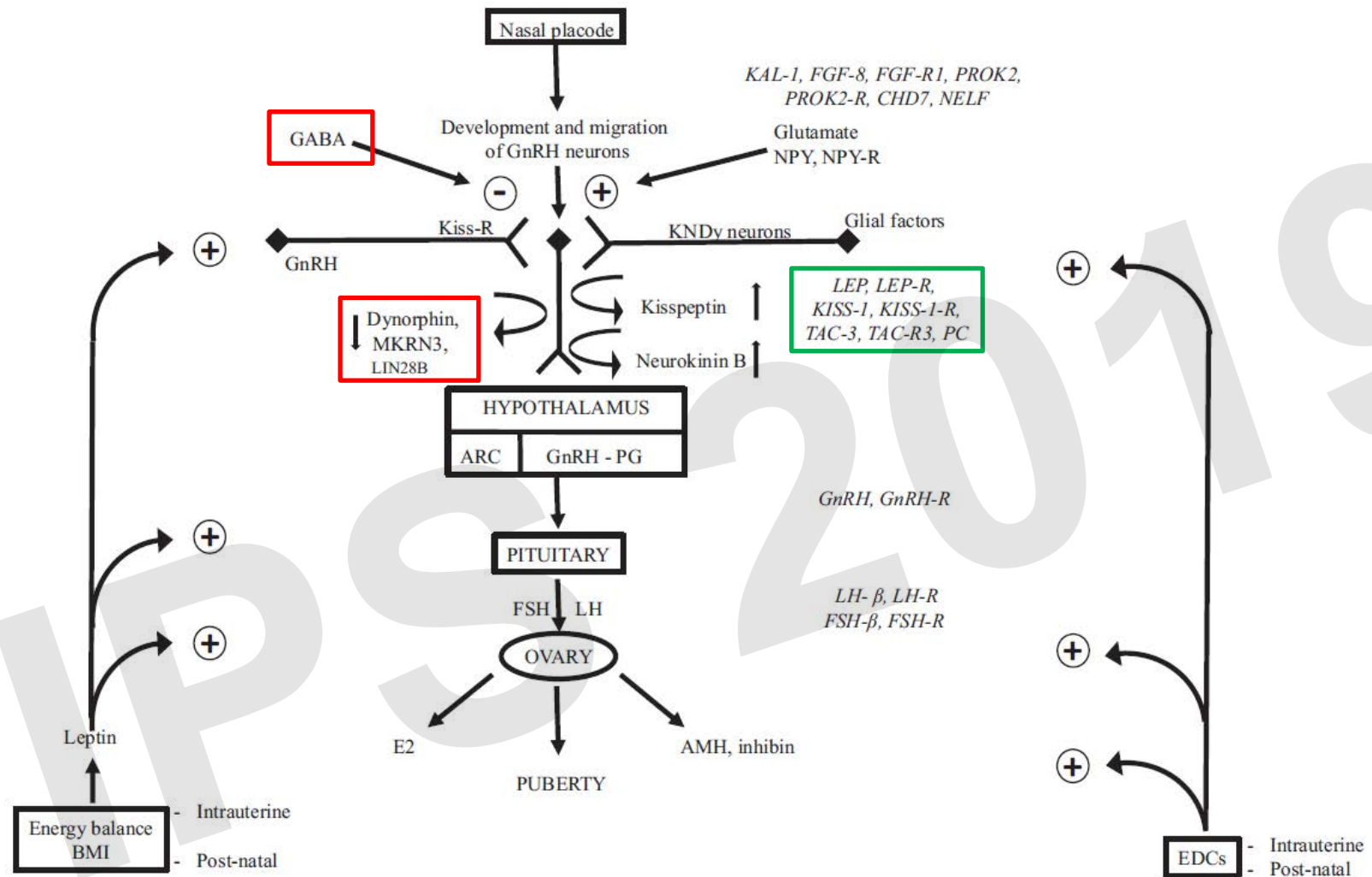Estrogen, Progestins
Testosterone, Inhibin

Heger, 2012

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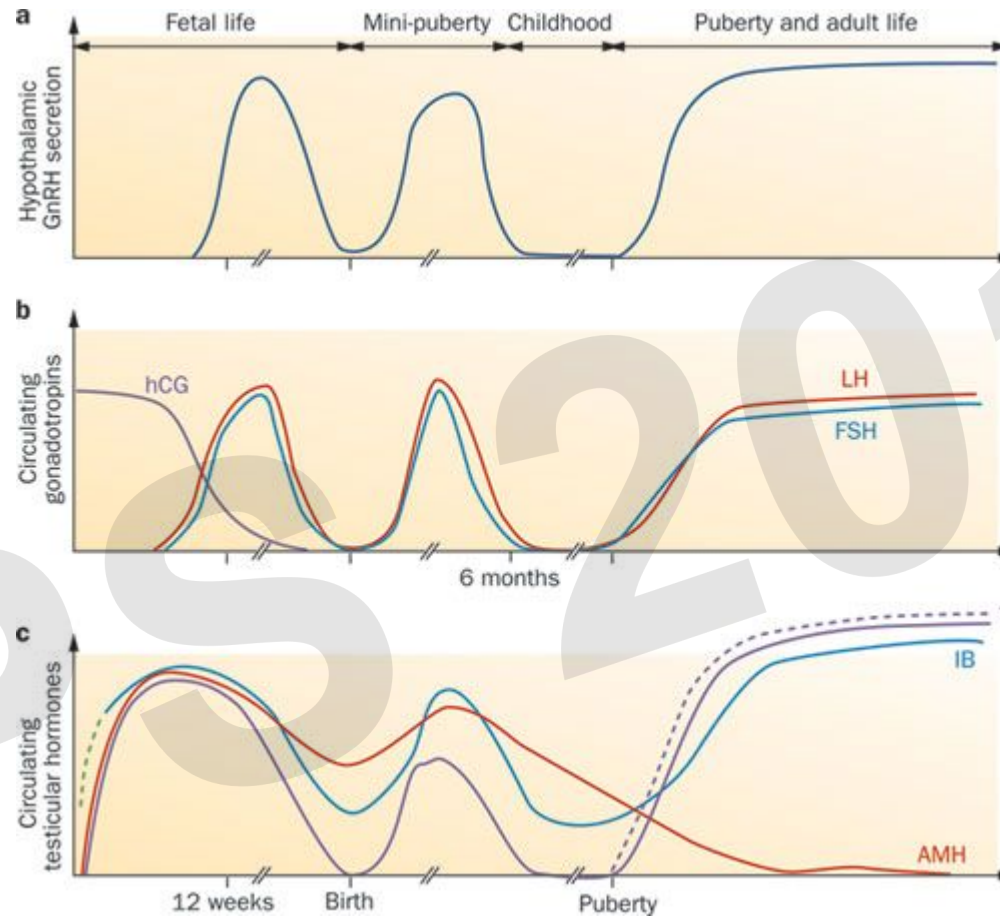
Gonadotropic axis regulation

Fig. 1. Neurosecretory control of the onset of puberty.

Sultan C, 2018

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Gonadotropic axis activation timing

Bouvattier 2012

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Gonadotropic hormone actions

Estradiol: female phenotype maturation

acceleration of growth

aromatase

Estrone: few
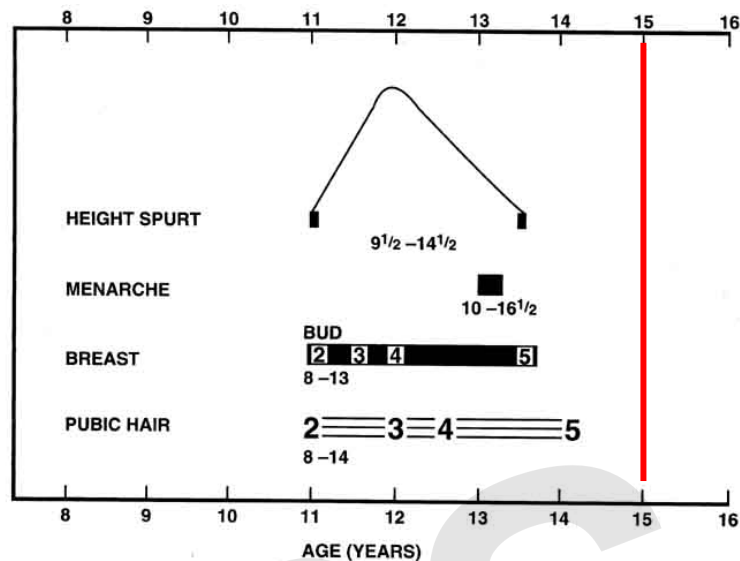
Testosterone: muscles, bones, internal genitals,
                        body hair, metabolism

Dihydrostestosterone: external genitals

DHEA: few
Androstenedione: body hair, sebum

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What is normal puberty?

For girls, TANNER 2 = BREAST = Accelerated growth

Menarche = 13 years
B2-B5 = 2.5 years
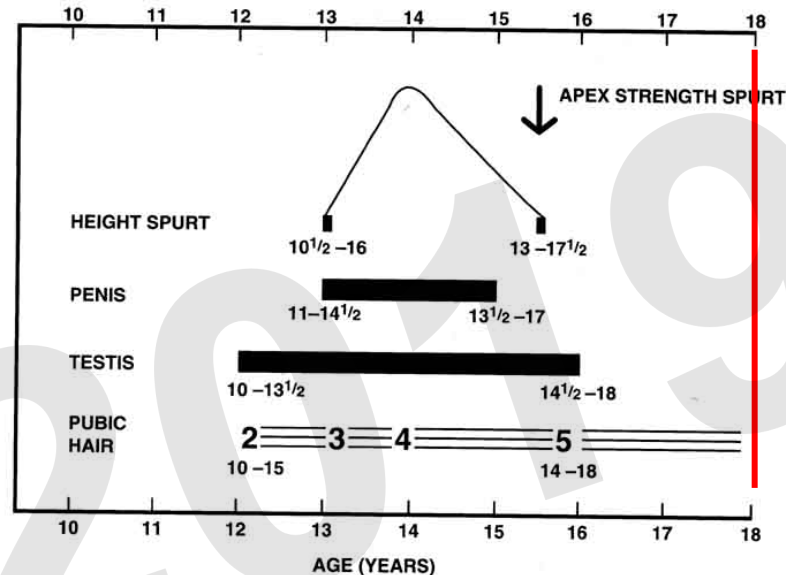
For boys, TANNER 2 = GONADS = Testis >3 mL

No accelerated growth (≥8 mL)

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What is normal puberty?
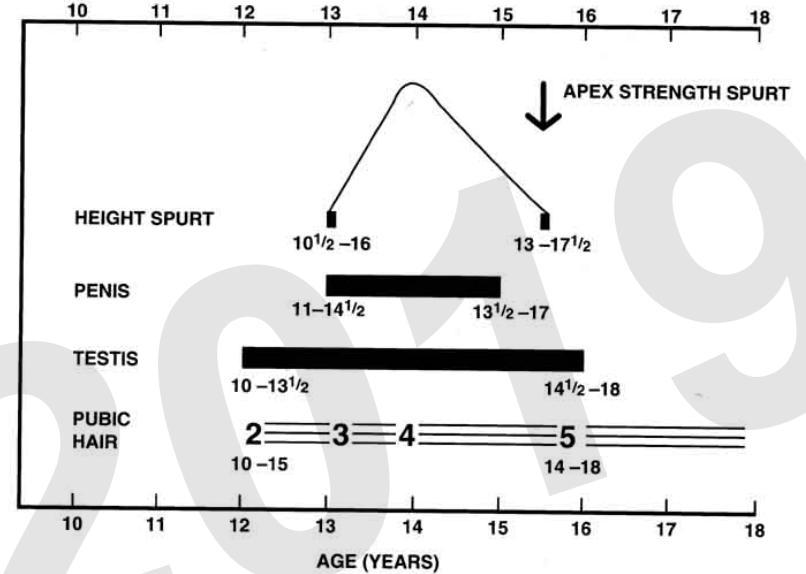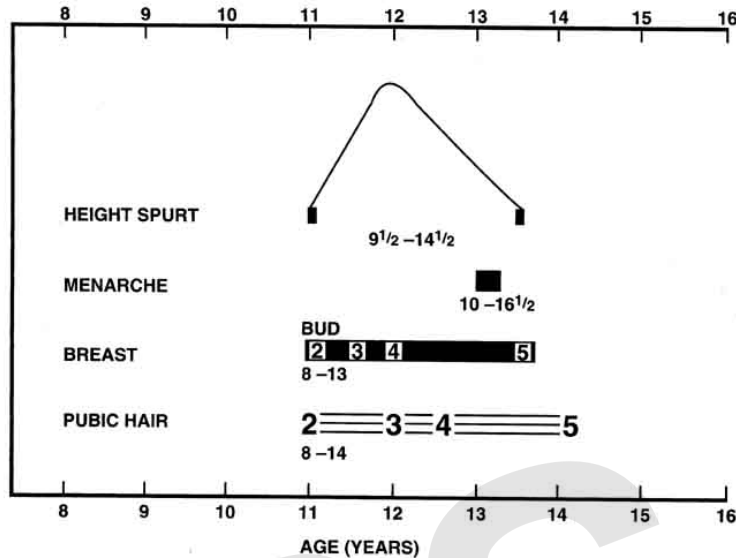
Body hair = presence of androgens BUT ≠ puberty

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What is normal puberty?

HEIGHT VELOCITY CURVES
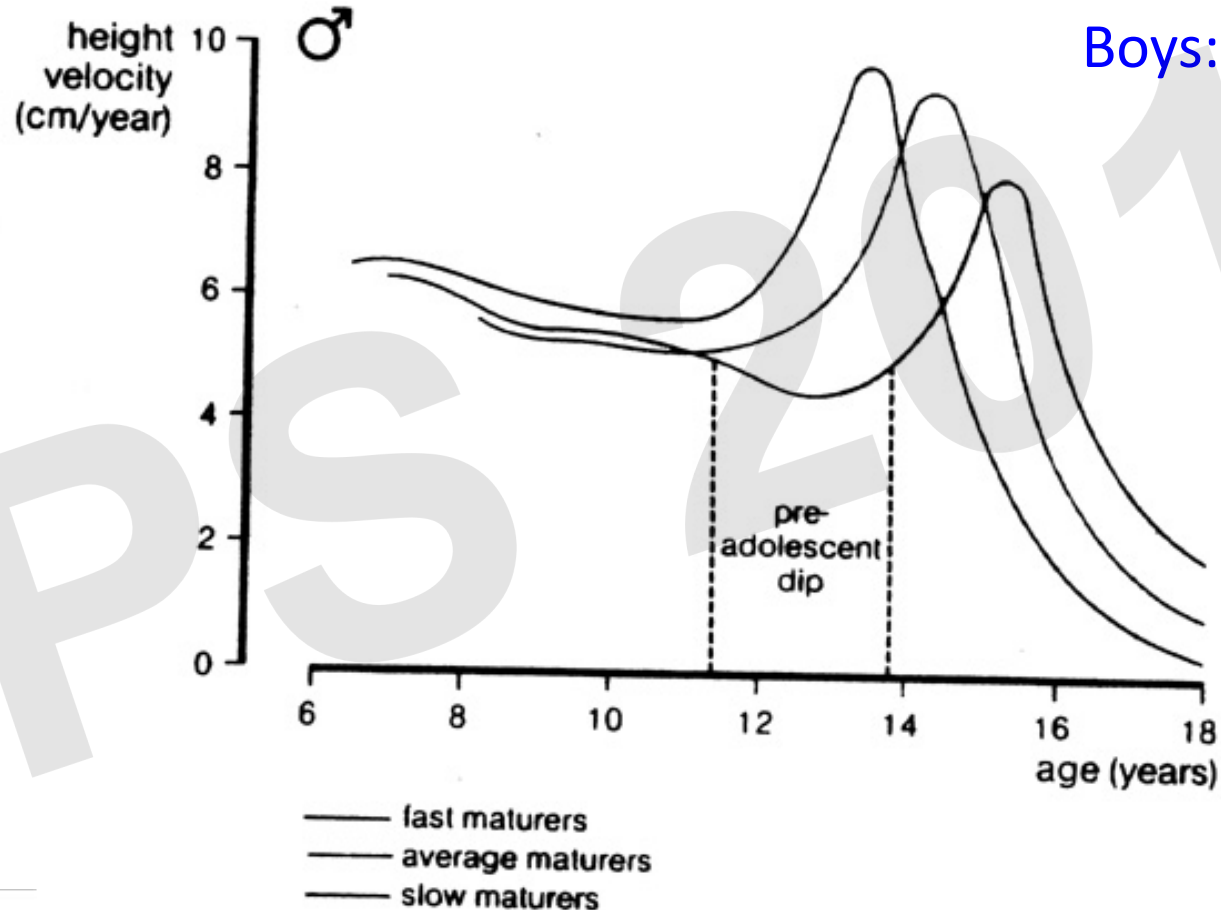
Girls: 20-25 cm
Boys: 25-30 cm

What is precocious puberty?

GIRLS: breast development < 8 years of age
menarche < 10 years of age

BOYS: testis > 3 mL < 9 years of age

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What is the reality in precocious puberty?
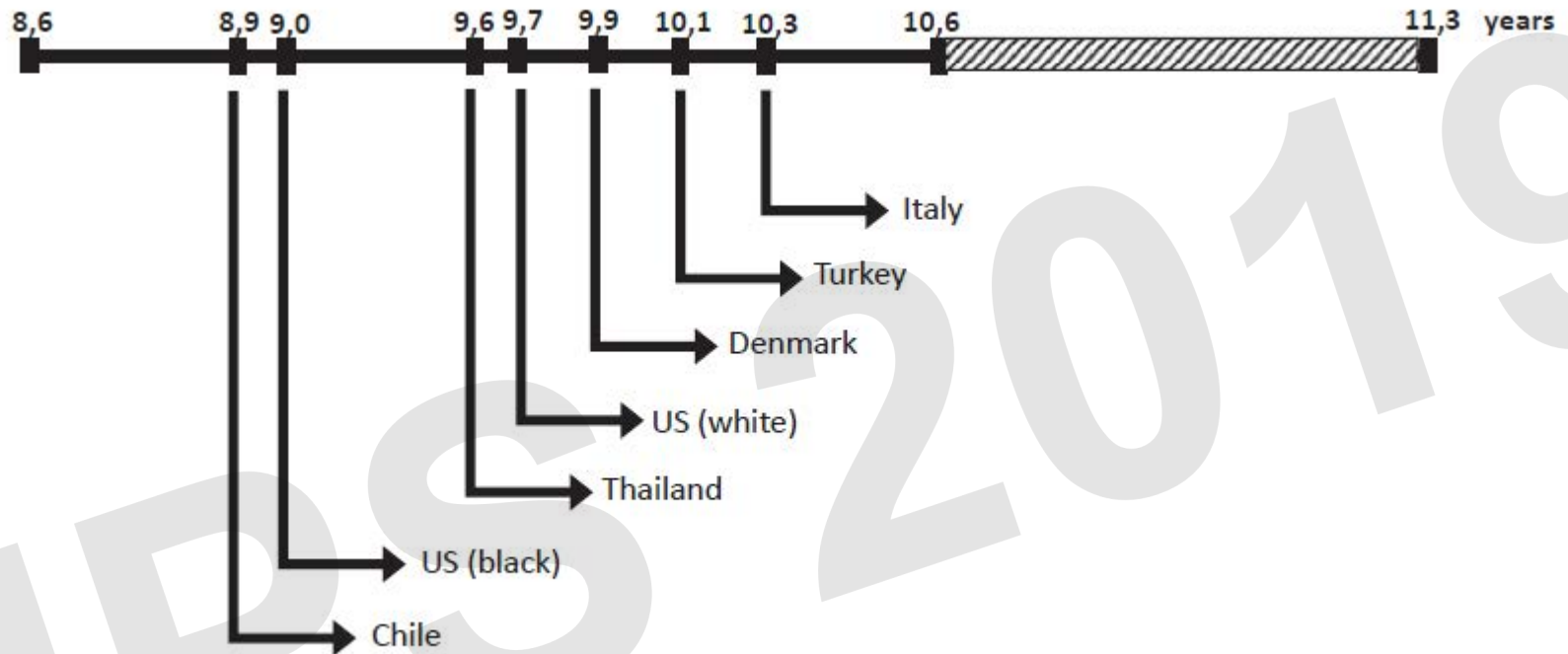
Fig. 2. Age at onset of puberty, as compared with Tanner stage B2.

Sultan C, 2018

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What is the reality in precocious puberty?
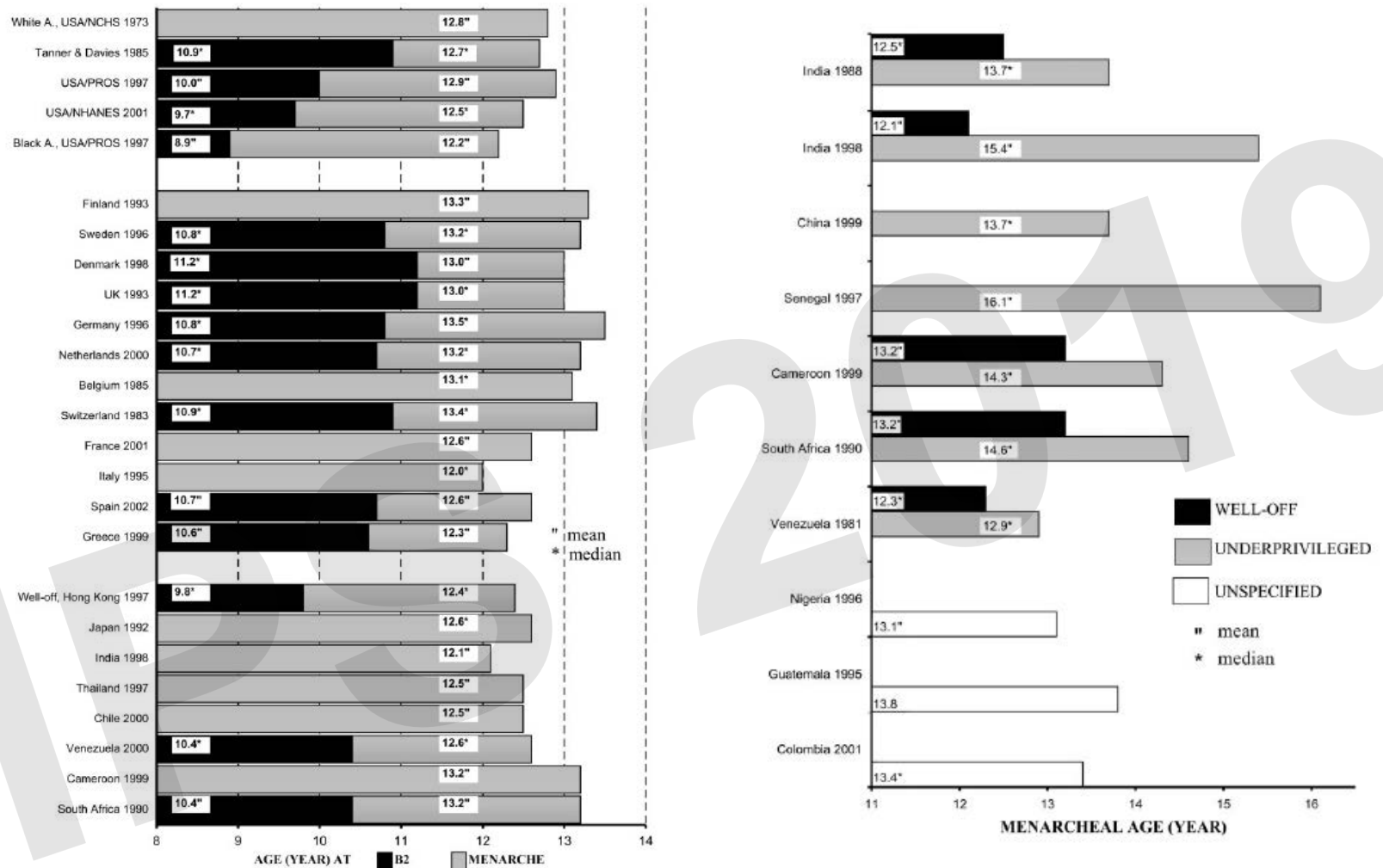
FIG. 2. Average (mean or median) ages at onset of breast development (B2) or menarche in different well-off populations around the world. The most recently published data were used to provide an update.

Parent AS 2003

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What causes precocious puberty?

Table 1
Classification of female precocious puberty.

1 Central precocious puberty, true precocious puberty: gonadotropin dependent
  a. Idiopathic
    - Typical form
    - Other clinical forms:
      - Extremely precocious puberty
      - Slowly progressive precocious puberty
      - Spontaneously regressive precocious puberty
      - Precocious puberty in adopted children
      - Familial central precocious puberty
      - Single advanced of puberty
      - Early puberty and growth retardation
      - Early puberty after premature pubarche
      - Early puberty in IUGR

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Girls: 70% idiopathic

Familial penetrance!

Favored by adiposity

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What causes precocious puberty?

b. Tumoral: CNS lesions (hamartoma, etc.)
c. Genetic forms of precocious puberty
d. Secondary to hypothyroidism, to peripheral precocious puberty
2. Incomplete isosexual precocity
   a. Isolated thelarche
   b. Isolated pubarche
   c. Isolated menarche
3. Peripheral precocious puberty, pseudo-precocious puberty
   a. Ovarian autonomous hyperactivity
   b. Peripheral hyperestrogenism: environmental endocrine disruptors

Boys: 70-90% Tumor → brain MRI

Girls: In the few studies stratified by age group, pooled prevalence was 25% in girls <6 years vs. 3% in girls 6-8 of age *(Cantas-Orsdemir S, JPEM 2018)*

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What causes precocious puberty?

CNS abnormalities

Hypothalamic hamartoma

Tumors: astrocytoma, ependymoma, optic or hypothalamic glioma, LH-secreting adenoma, pinealoma, neurofibroma, non-hCG secreting dysgerminoma, craniopharyngioma*

Other congenital malformations: suprasellar cyst, arachnoid cyst, septo-optic dysplasia, hydrocephalus, *spina bifida*, vascular malformation, meningomyelocele, ectopic posterior pituitary lobe, pituitary duplication

Acquired diseases*: inflammatory processes (abscess, meningitis, encephalitis, sarcoidosis, tuberculosis), radiation, perinatal asphyxia, trauma

Brito 2016

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What causes precocious puberty?

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b. Tumoral: CNS lesions (hamartoma, etc.)
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3. Peripheral precocious puberty, pseudo-precocious puberty
  a. Ovarian autonomous hyperactivity
  b. Peripheral hyperestrogenism: environmental endocrine disruptors

Genetics: early and/or familial

KISS1, KISS1R, MKRN3

Secondary: always screen TSH levels

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Clinical diagnosis of precocious puberty

Girls: breast development

                     accelerated growth

                     neurological, vision, skin, virilization

Early = exposure to exogenous estrogens?

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Clinical diagnosis of precocious puberty

Girls & Boys: accelerated bone maturation
                       BA = CA + 1 year
                       or BA/CA >1.2

Girls: pelvic ultrasound
                             uterine length (volume)
                             uterine form
                             ovarian volume & structure
                             fundus/cervix ratio

                             tumor, cyst

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Clinical diagnosis of precocious puberty

TABLE I–*Ovarian Volume, Uterine Length and FCR According to Chronological Age (n = 214)*

Age group	n	Ovarian volume (cm^3)		Uterine length (cm)		FCR	
		Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median
<30 days	10	0.25 (0.25)	0.15	2.98 (0.25)	2.95	0.79 (0.28)	0.66
4-8 months	10	0.21 (0.19)	0.13	2.72 (0.61)	2.75	0.86 (0.19)	0.81
1-2 yr	10	0.24 (0.23)	0.14	2.50 (0.44)	2.40	1.00 (0.20)	1.00
2-3 yr	10	0.28 (0.15)	0.27	2.56 (0.46)	2.45	0.91 (0.19)	0.93
3-4 yr	10	0.36 (0.22)	0.26	2.48 (0.63)	2.55	0.99 (0.21)	1.06
4-5 yr	10	0.50 (0.32)	0.36	2.84 (0.37)	2.85	1.03 (0.25)	1.00
5-6 yr	10	0.51 (0.13)	0.53	2.83 (0.47)	2.85	0.91 (0.22)	0.92
6-7 yr	15	0.51 (0.35)	0.37	3.01 (0.27)	3.00	1.03 (0.34)	1.00
7-8 yr	10	0.62 (0.54)	0.52	3.02 (0.21)	3.00	1.16 (0.58)	1.10
8-9 yr	10	1.22 (0.59)	1.24	3.23 (0.41)	3.25	1.35 (0.51)	1.18
9-10 yr	11	1.23 (1.50)	0.90	3.71 (0.88)	3.30	1.30 (0.57)	1.20
10-11 yr	15	1.34 (0.54)	1.51	3.59 (0.69)	3.40	1.21 (0.30)	1.22
11-12 yr	15	1.64 (1.32)	1.42	4.80 (1.69)	5.30	1.28 (0.33)	1.22
12-13 yr	15	2.97 (1.57)	2.97	5.50 (1.27)	5.30	1.48 (0.33)	1.50
13-14 yr	11	3.38 (1.51)	3.03	6.06 (0.42)	6.00	1.56 (0.39)	1.63
14-15 yr	10	4.29 (2.73)	4.17	6.16 (0.81)	6.25	1.71 (0.39)	1.53
15-16 yr	12	4.44 (1.85)	4.00	6.94 (1.12)	7.10	1.73 (0.43)	1.68
16-17 yr	10	4.51 (1.41)	4.96	7.03 (0.9)	7.20	1.80 (0.40)	1.68
17-18 yr	10	5.42 (2.25)	4.97	8.00 (1.65)	7.55	1.56 (0.31)	1.58

Khadilkar 2006

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Clinical diagnosis of precocious puberty

TABLE II–*Age, Number, Ovarian Volume, Uterine Length, FCR and Endometrial Thickness According to Breast Stage*

Breast staging	n	Age (yr) Mean	Ovarian volume (cm³) Mean (SD)	Ovarian volume (cm³) Median	Uterine length (cm) Mean (SD)	Uterine length (cm) Median	FCR Mean (SD)	FCR Median	Endometrial thickness Mean (Range) mm
1	119	5	0.52*(0.45)	0.36	2.90*(0.53)	2.90	1.01*(0.40)	1.00	0.1 (0-3)
2	17	10	1.29 (0.57)	1.37	3.7 0(0.82)	3.30	1.29 (0.40)	1.28	1.1 (0-2)
3	12	12	2.09 (1.39)	1.78	4.81 (1.28)	4.85	1.38 (0.30)	1.31	2.0 (0-5)
4	10	12	3.32 (1.80)	2.74	5.87 (1.34)	5.65	1.54 (0.30)	1.55	3.1 (0-6)
5	56	15	4.34 (2.01)	3.93	6.84 (1.18)	6.60	1.67 (0.40)	1.61	5.2 (0-9)
p			<0.001	<0.001	<0.001				

p significantly different for measurements at each breast staging, * Significantly different than breast staging 2,3, 4 and 5 at $p<0.001$.

Khadilkar
2006

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Clinical diagnosis of precocious puberty

ULTRASOUND

Uterine length: 3.4-4 cm = intermediate (primed)

4 cm = pubertal

Fundus/cervix ratio >1 = pubertal

Ovarian volume > 1.4-1.5 mL = pubertal

De Vries 2011; Ersen JPEM 2012

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Clinical diagnosis of precocious puberty

Table 2. Cutoff values of basal and GnRH-stimulated LH for diagnosis of central precocious puberty

Author	Method	Basal LH (IU/L)	GnRH	LH peak after GnRH (IU/L)
Neely and cols., 1995 (32)	ICMA	0.15	Gonadorelin 100 ug IV	5.0
Brito and cols., 1999 (27)	IFMA	0.6	Gonadorelin 100 ug IV	6.9 (F) 9.6 (M)
Brito and cols., 2004 (30)	IFMA	0.6	Leuprorelin acetate 3.75 mg	10.0
Houk and cols., 2009 (33)	ICMA IFMA	0.83 1.05	N/A	N/A
Pasternak and cols., 2012 (34)	ICMA	0.1	Gonadorelin 100 ug IV	4.9
Sathasivam and cols., 2010 (35)	ICMA	0.3	Leuprorelin acetate 20 ug/kg SC	5.0
Resende and cols., 2007 (28)	ICMA IFMA	0.2 0.6	Gonadorelin 100 ug IV	4.1 (M); 3.3 (F) 3.3 (M); 4.2 (F)
Lee and cols., 2013 (36)	ECLIA	0.1	Gonadorelin 100 ug IV	5.0 (F)
Freire and cols., 2013 (37)	IFMA ECLIA	N/A	Triptorelin 0.1 mg/m^2, maximum of 0.1 mg SC	7.0 8.0
Bizarri and cols., 2014 (38)	ICMA	> 0.2	Gonadorelin 100 ug IV	5.0

ICMA: immunochemiluminescence; IFMA: immunofluorimetric; ECLIA: eletrochemiluminescence; SC: subcutaneous; IV: intravenous; F: female; M: male; N/A: not available.

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Clinical diagnosis of precocious puberty

CUT-OFF VALUES FOR BASAL AND STIMULATED LH

Basal LH: 0.3 IU/L

Stimulated: >6 IU/L

LH >0.6 x FSH ?
LH >FSH ?

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Discrimination of CPP from premature thelarche

	Premature thelarche	CPP
Growth velocity	Normal	Accelerated
Bone maturation	Normal	Accelerated
Vaginal mucosae	Red	Pink
Pelvic US	Prepubertal	Pubertal
Areolas	Poorly developed	Enlarged
Response to GnRH	Prepubertal	Pubertal
Plasma estrogens	Undetectable	Sometimes detectable

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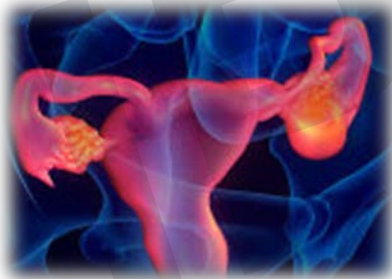
Peripheral puberty
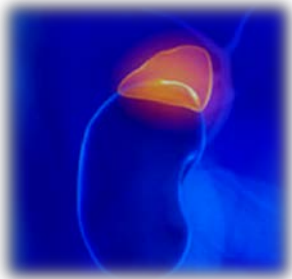
Congenital adrenal hyperplasia
>> -> virilization only

Adrenal tumors
>> -> androgens, estrogens (extremely rare)

Ovarian cysts
>> benign, isolated -> Mc Cune Albright

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McCune Albright syndrome

GNAS mutation

Hyperfunction of endocrine tissues

Osteodysplasia

Suppressed gonadotrophins

Reduced testicular volume

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GnRH agonist treatment: indications

Table 5. Criteria for identifying girls who are likely to have progressive precocious puberty

Progression of breast staging in less than 3-6 months

Growth velocity > 6 cm/year

Bone age advancement of more than 1.5-2 years

PAH below target height and decline in PAH during follow-up

Uterine volume > 2.0 mL, long diameter > 35 mm, presence of endometrial echo

Ovarian volume > 2-3 mL

Peak LH > 5.0 mIU/L at GnRH test, peak LH/FSH ratio > 0.66
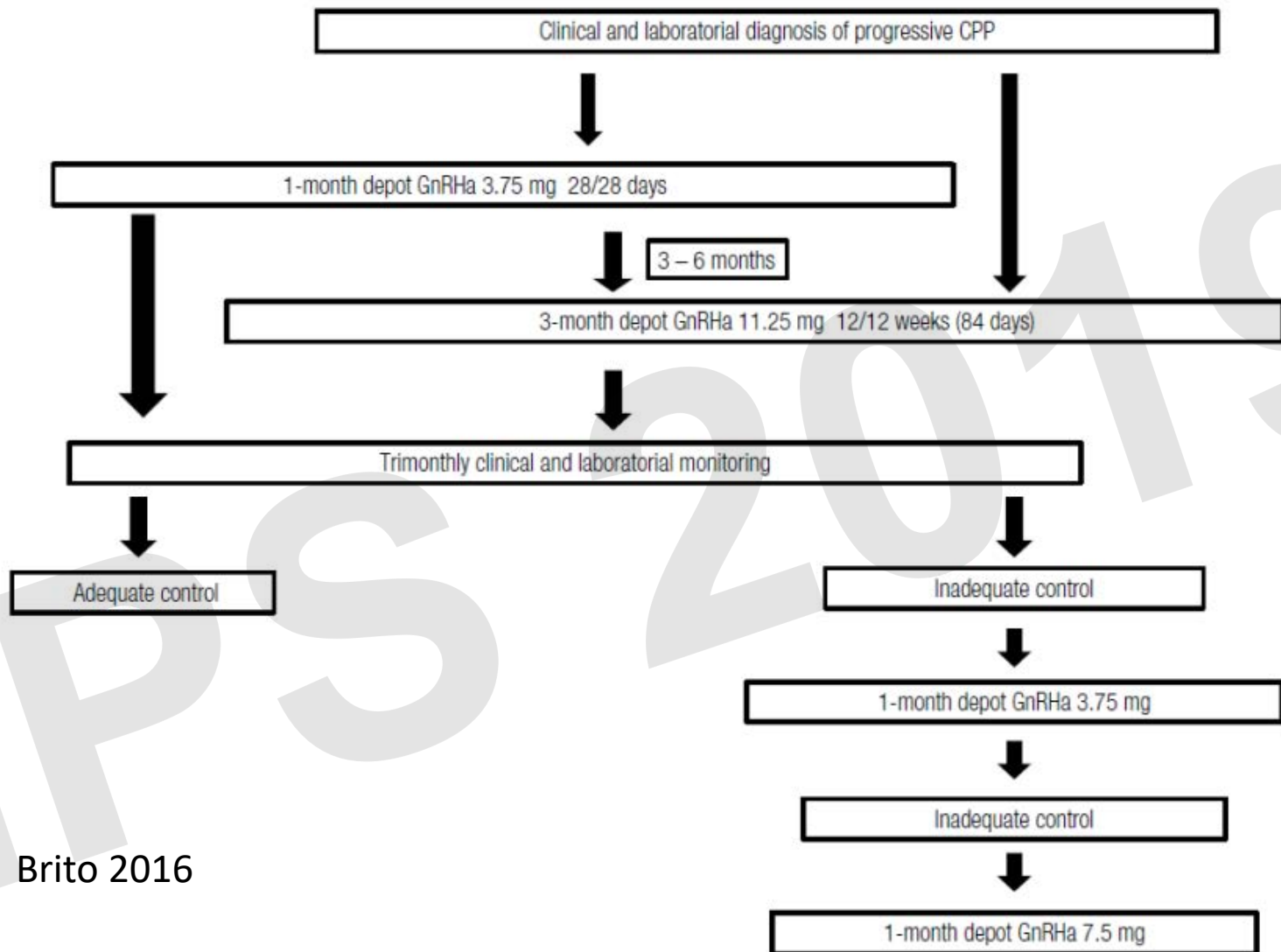
Basal LH > 0.3 mIU/L, detectable basal E2

PAH: predicted adult height, LH: lutenizing hormone, GnRH: gonadotropin-releasing hormon, FSH: follicle-stimulating hormone, E2: estradiol

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GnRH agonist treatment: flow chart

Clinical and laboratorial diagnosis of progressive CPP

1-month depot GnRHa 3.75 mg 28/28 days

3 – 6 months

3-month depot GnRHa 11.25 mg 12/12 weeks (84 days)

Trimonthly clinical and laboratorial monitoring

Adequate control

Inadequate control

1-month depot GnRHa 3.75 mg

Inadequate control

1-month depot GnRHa 7.5 mg

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GnRH agonist treatment: outcomes

Table 3. Effect of age of onset of treatment on height (studies with no control group)

	CA at onset		BA at onset		< 6 yr			> 6 yr		
	< 6 yr	> 6 yr	< 6 yr	> 6 yr	PAH	TH	FH	PAH	TH	FH
Partsch et al (16)	5.0 ± 0.4	7.8 ± 0.2	8.4 ± 0.5	10.4 ± 0.3	152.1 ± 2.2	162.4 ± 1.08	161.6 ± 1.43	157.7 ± 1.8	165.3 ± 1.43	159.4 ± 1.75
Lazar et al (17)	6.4 ± 1.2	7.5 ± 0.6	11.3 ± 0.4	11.3 ± 0.3	154.6 ± 6.6	159.3 ± 5.0	162.8 ± 5.0	157.8 ± 5.2	153.7 ± 6.7	157.9 ± 5.1

CA: chronological age, BA: bone age

Bereket 2018

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GnRH agonist treatment: outcomes

Before the age of 6 years:

       -> treatment may have auxological impact

After the age of 6 years:

       -> psychological indication (even after menarche)

Long-term impact (bone health, fertility)?

       -> uncertain

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+ PEDI members !

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BESPEED

ISPAD International Society for Pediatric and Adolescent Diabetes

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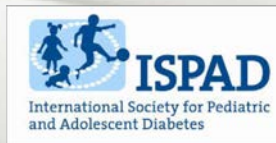UCL Université catholique de Louvain

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IPS 2019

Underlying causes of premature pubarche

Increasing levels of androgens ↓

Idiopathic premature pubarche: Androgens and DHEAS normal, LH/FSH normal, BA = CA *(increased sensitivity of the androgen receptor)*

Idiopathic premature adrenarche *(Androgens and DHEAS slighty elevated, appropriate for Tanner II-III, LH/FSH normal, BA>CA, growth acceleration)*

Apparent DHEA sulfotransferase deficiency *(inappropriate conversion of DHEA to the inactive DHEAS)*

Apparent cortisone reductase deficiency *(increased conversion of cortisol to its less active form cortisone, resulting in ACTH-mediated adrenal hyperplasia)*

Late-onset AGS *(e.g.21-Hydroxylase deficiency)*
Androgen producing tumours